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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/426,038	10/25/1999	JESPER VIND	5579.210-US	1334

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EXAMINER
PONNALURI, PADMASHRI

ART UNIT	PAPER NUMBER
1627	11

DATE MAILED: 12/04/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/426,038	Vind
Examiner	**Art Unit**
Padmashri Ponnaluri	1627

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Sep 7, 2001* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-22 and 27-30* is/are pending in the application.

4a) Of the above, claim(s) *10, 19, 22, and 27-29* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-9, 11-18, 20, 21, and 30* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. The amendment filed on 9/7/01 has been fully considered and entered into the application.

2. New claim 30 has been added by the amendment filed on 9/7/01.

3. Claims 1-22, 27-30 are currently pending in this application.

4. Claims 22, 27-29 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention. Election was made **without** traverse in Paper No. 7.

5. Claims 10, 19 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected species. Election was made **without** traverse in Paper No. 7.

6. Claims 1-9, 11-18, 20-21, 30 are currently being examined in this application.

7. The lack of written description rejection of claims 1-9, 11-21 has been withdrawn in view of applicants amendments and arguments.

8. Claims 1-9, 11-18, 20-21, and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of the replication initiating sequence set forth in SEQ ID NO 1 or SEQ ID NO 2, does not reasonably provide enablement for any fungal replication initiating sequence in the vectors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The instant claims briefly recite a method of constructing and selecting a library of polynucleotide sequences of interest in filamentous fungal cells, comprising; a) transforming fungal cells with a population of DNA vectors, wherein each vector comprises a polynucleotide sequences encoding fungal selection marker and fungal replication initiating sequences; and a polynucleotide sequence of interest, b) cultivating the cells, c) selecting one or more transformants expressing a desired characteristics, d) isolating the transformants of interest.

The specification does not sufficiently teach the use of any replication initiating sequence other than the sequences having at least 80 % identity with the nucleic acid sequence of SEQ ID NO 1 or SEQ ID NO 2, claimed by the instant claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (U.S.P.Q. 2d 1400 (CAFC (1988)). The factors to be considered include; the quantity of experimentation necessary, the amount of guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the predictability of the art and the breadth of claims.. The factors most relevant to this rejection are the scope of the claim, unpredictability in the art, the amount of experimentation required, and the amount f direction or guidance presented.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation. Besides the polynucleotides with the sequences with 80 % identity with the SEQ ID NO:1 and SEQ ID NO:2, the specification fails to provide guidance as to how to make or use any replication initiating

sequence. The replication initiating sequence used in the method is either polynucleotide of sequence of SEQ ID NO:1 or SEQ ID NO: 2, or the sequence which hybridizes with nucleic acid sequence of SEQ ID NO: 1 or SEQ ID NO: 2. The specification discloses (page 13), and claims 12-13 recite that the degree of identity is determined by the computer programs known in the art such as GAP. However, claims 1-9, 11, 18, 20-21 do not disclose the replication initiation sequence, and thus the scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of nucleic acid sequences broadly encompassed by the claims due to the significant number of untaught sequences. The use of "percent" (in claims 12-17) in conjunction with any of the various terms that refer to sequence similarity is a problem since sequence identity between two sequences has no common meaning within the art. The term "percent" can be defined by the algorithm and parameter values set when using the algorithm used to compare the sequences. The scoring of gaps when comparing one sequence to another introduces uncertainty as to the percent of similarity between two sequences. Since the nucleic acid sequence of a polynucleotide determines its protein coding properties, predictability of which changes can be tolerated in a polynucleotide's nucleic acid sequence and still retain similar functions and properties requires a knowledge of, and guidance with regard to which nucleic acids in the nucleotide sequence, if any are tolerant of modification and which are conserved (i.e., ., expectedly intolerant to modification), and detailed knowledge of the ways in which the product's structure relates to its functional usefulness. However, the problem of predicting functional aspects of the product from mere sequence data of a single nucleic acid

sequence and what changes can be tolerated is complex and well outside the realm of routine experimentation. Therefore, there is no evidence of record to show that one skilled in the art would be able to practice the invention as claimed without an undue amount of experimentation.

In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-9, 11-18, 20-21, 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite by reciting a method of constructing and selecting or screening a library. It is not clear whether claim is drawn t a method of constructing or selecting library. Applicants are requested to amend the claim to recite one single method.

Claim 1 recites 'selection pressure', clarification is requested what does applicants mean by selection pressure. The specification in pages 9-10 does not have clear definition for 'selection pressure' , it is not clear whether applicants mean in presence of an effective amount

of appropriate selective agent, which is selected based on the selection marker. Applicants are requested to amend the claims such that the cells are cultivated in presence of selection agent.

Claim 1 recites 'desired characteristic', clarification is requested what does applicants mean by desired characteristics. The specification does not recite a definition for the desired characteristic. Applicants are requested to clarify.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the instant claim does not recite method steps, how to select or screen for one or more transformants expressing a desired characteristics. Since it is not even known what is desired characteristics applicants are looking for, it is not clear how to select for a transformants expressing desired characteristics.

Claim 4 recites 'a portion thereof', clarification is requested which portion applicants are referring to. It is not clear whether the portion of the enzyme or receptor or antibody has any specific function or structure. The specification disclosure does not have nay definition for the portion thereof.

Claims 12-16 are indefinite by recitation of "% identity. The use of such terms as percent homology, percent similarity, and percent identity in connection with nucleic acid sequence is vague and indefinite in the absence of a clear description or definition of what the term means. This is because sequence identity between two sequences has no common meaning within the art. Although the methods for determining identity between two sequences, such as the

use of programs like BLAST, BLASTIN, or FAST, as disclosed on page 13, and the disclosure do not adequately describe how the applicants themselves determined the percent identity. The disclosure does not allow one skilled in the art to determine the existence of gaps, or which mismatches, alterations or mutations are encompassed by the claims. It is therefore unclear what isolated sequences the applicants claim.

Claim 18 recites the limitation "wherein the modification of parent polynucleotide sequence " in lines 1-2. There is insufficient antecedent basis for this limitation in the claim or in claim 2.

Claim 18 recites 'preferably' which is indefinite. Applicants are requested to clarify.

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 1-9, 11, 18-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Christensen (WO 98/01470) and Dalboge et al (Mol. Gen. Genet (1994) 243: 253-260.).

Christensen discloses that a transcription factor regulating alpha amylase promoter initiated expression in filamentous fungi, especially in Aspergilli, (refers to instant claim 20) DNA sequences encoding for said factor, its transformation into and expression in fungal host organisms, and the use of said factor (see the abstract). The reference discloses a method of producing a filamentous fungal cell comprising the introduction of a DNA fragment coding for

any such factor in to a filamentous fungus, wherein alpha amylase promoter or a co-regulator promoter regulates the expression of a polypeptide of interest in a manner whereby said promoter will be expressed in said fungus (see pages 3-4) (refers to instant claim 1). The reference discloses that DNA sequence encoding transcription factor homologous to the transcription factor of the invention, the DNA sequences may be derived by similar screening of cDNA library of another microorganism. The reference discloses that the method of producing a filamentous fungal host cell comprising the introduction of any of the DNA fragments into a filamentous fungus wherein the alpha amylase promoter or another coregulated promoter regulates the expression of a polypeptide of interest in a manner whereby said factor will be expresses in said fungus (see page 12, lines 29-34). The reference discloses that the invention provides a recombinant expression vector comprising DNA construct of the invention (see page 13, lines 4-5). The reference discloses the promoters for use in filamentous fungal cells (see pages 13-14) (refers to instant claim 8). The reference discloses a method of producing a polypeptide of interest, whereby a host cell is grown under conditions conductive to the production of said factor and said polypeptide of interest, and the polypeptide of interest is recovered (see page 15) (refers to instant claim 1, steps b and c). The reference discloses that the method may also be used for production of industrial enzymes such as hydrolases (see page 15) (refers to instant claim 4-5), and proteases (see page 16, line 1) (refers to instant claim 6). The reference teaches that the transcription factor is used to identify the sequences which bind to alpha amylase promoter to which it binds, by using GST fusion protein .

The claimed invention differs from the prior art teachings by reciting that the vector comprises a fungal selection marker. Christensen teaches a method of producing a filamentous fungal cell comprising the introduction of a DNA fragment coding for any such factor in to a filamentous fungus, wherein alpha amylase promoter or a co-regulator promoter regulates the expression of a polypeptide of interest in a manner whereby said promoter will be expressed in said fungus. The reference teaches the use of GST fusion protein. The reference does not use a fungal selection marker. However, it is known to use different markers in the vectors, such that the cells would be grown in a selective medium, in which particular cells of interest would be able to grow well or distinguish themselves from the others. Dalboge et al teach novel method for efficient expression cloning of fungal enzyme genes. The reference teaches a cloning system which is independent of specific yeast strains and thus can be applied to non-essential enzymes. The flow diagram in Fig.1 teaches the disclosed method. The reference teaches a method for expression of cloned genes in Aspergillus. The reference teaches that vector pHD414 was introduced into a A.oryzae by cotransformation with amdS gene containing plasmid (which refers to the selection marker of the instant claims). The reference teaches that the transformants are isolated and assayed for enzyme activity. Thus, it would have been obvious to one skilled in the art at the time the invention was made to use a fungal selection marker in the vectors of Christensen, such that the fungal cells having the gene of interest is identified under specific growth conditions in which the selection marker is expressed. A person skilled in the art would

have been motivated to use a fungal selection marker in the vectors taught by Christensen so that the cells carrying the gene of interest would be identified.

13. Applicant's arguments with respect to claims 1-9, 11-21 have been considered but are moot in view of the new ground(s) of rejection.

14. No claims are allowed.

15. The following is a statement of reasons for the indication of allowable subject matter: the claimed method in claims 12-14 and 17 is neither taught nor suggested by the prior art. The prior art of record do not teach the use of replication initiating sequence of SEQ ID NO: 1, or SEQ ID NO: 2 in the vectors, which are used in method of screening a library of polynucleotides of interest as claimed.

Any inquiry concerning this communication should be directed to P. Ponnaluri whose telephone number is (703) 305-3884. The examiner can normally be reached on Monday through Friday from 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat, can be reached at (703)308-2439. The fax number for this group is (703)305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist whose telephone number is (703)308-0196.

P. Ponnaluri
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Technology center 1600
Art Unit 1627
01 December 2001

PADMASHRI PONNALURI
PRIMARY EXAMINER